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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,563	GUTHRIE ET AL.	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,20-23,25, and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,20-23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks filed 29 May 2007 are duly acknowledged and made of record. Applicants have submitted arguments directed to (1) the alleged lack of motivation to combine between the references Manthey et al. and Bok et al. Applicants cite that these individual references are directed to treatment of unrelated diseases (instant Remarks, page 5, 2nd full paragraph, line 3). Additionally, Applicants submit that (2) the Malterud reference fails to teach or suggest a method for treating a mammal having abnormalities resulting from insulin resistance. Further, Applicants submit the combination of the Pershadsingh et al. and Robbins et al. references are unfounded due to the failure to teach or suggest the presently claimed methods.

Applicants' arguments are acknowledged, however, they are not found persuasive.

Malterud et al. teach each and every polymethoxylated flavonoid as disclosed, such as sinensetin, nobiletin, tangeretin, heptamethoxvflavone and tetramethylscutellarein (instant claim 15), which have been isolated from orange peels and collectively are inhibitors of 15 lipoxygenase (Malterud et al. Inhibitors of 15-lipooxygenase from orange peel. J Agric Food Chem (2000 Nov); 48(11): 5576-80, printed page: 1, Abstract, lines 1-3).

Accordingly, Manthey et al. adequately teach the central issue of claimed invention in conjunction with Bok et al. The motivation to combine Manthey and Bok is directed to their related teachings of treating certain disease states with certain combinations of polymethoxyflavones. Accordingly, related etiological processes govern these disease states, in some instances, as disclosed in the previous Action to applicant.

Furthermore, Type 2 diabetes is associated with significantly accelerated rates of macrovascular complications such as atherosclerosis. Accordingly, atherosclerosis is an

inflammatory disease and that certain inflammatory markers may be key predictors of diabetic atherosclerosis. Proinflammatory cytokines and cellular adhesion molecules expressed by vascular and blood cells during stimulation by growth factors and cytokines-seem to play major roles in the pathophysiology of atherosclerosis and diabetic vascular complications. However, [...], data suggests that inflammatory responses can also be elicited by smaller oxidized lipids that are components of atherogenic oxidized low-density lipoprotein or products of phospholipase activation and arachidonic acid metabolism. These include oxidized lipids of the lipoxygenase and cyclooxygenase pathways of arachidonic acid and linoleic acid metabolism. These lipids have potent growth, vasoactive, chemotactic, oxidative, and proinflammatory properties in vascular smooth muscle cells, endothelial cells, and monocytes. Cellular and animal models indicate that these enzymes are induced under diabetic conditions, have proatherogenic effects, and also mediate the actions of growth factors and cytokines. [The above disclosure] highlights the roles of the inflammatory cyclooxygenase and 12/15-lipoxygenase pathways in the pathogenesis of diabetic vascular disease. Evidence suggests that inflammatory responses in the vasculature can be elicited by small-oxidized lipids that are components of oxidized low-density lipoprotein or products of the lipoxygenase and cyclooxygenase pathways of arachidonic and linoleic acid metabolism. This review evaluates these inflammatory and proatherogenic pathways in the pathogenesis of diabetic vascular disease (Natarajan et al., Lipid Inflammatory Mediators in Diabetic Vascular Disease, Arteriosclerosis, Thrombosis, and Vascular Biology, 2004; 24:1542, printed pages 1 and 2, see pages 1 and 2) (page 5 and 6 of previous Office Action).

Still further, instant new claim 26 discloses a method of treating a mammal having metabolic abnormalities resulting from insulin resistance comprising orally administering a solid or liquid composition comprising an effective amount of a polymethoxyflavone composition consisting *essentially of nobiliten and tangeretin*, wherein said polymethoxyflavone composition is administered to said mammal in an amount of up to 5000 mg/day or up to 70 mg/kg/day, based on the weight of said mammal, said composition reducing serum insulin levels by at least about 26%.

In response, the phrase, 'an effective amount of a polymethoxyflavone (PMF) composition consisting *essentially of nobilten and tangeretin'* is noted, however, it still suggests or supports nothing to the exclusion of the other said PMF's as disclosed in instant claim 2. The phrase 'administering a solid or liquid composition ***comprising*** *an effective amount of a polymethoxyflavone composition* ***consisting*** *essentially* [...].' Additionally, though the polymethoxyflavone composition may consist essentially of nobilten and tangeretin, the overall composition itself is still open to the inclusion of additional elements due to the use of "comprising" in the description of the solid or liquid composition.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 15, 20-23, 25, and 26 are pending for prosecution on the merits.

Claims 1-14, 16-19, and 24 have been cancelled.

Claim Rejection, 35 U.S.C.§ 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 and 20-23 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malterud et al. (Inhibitors of 15-lipooxygenase from orange peel. J Agric Food Chem (2000 Nov); 48(11): 5576-80, printed page: 1, Abstract, lines 1-6 and lines 17-21) and Manthey et al. (USPN 6,184,246 B1) in view of Bok et al. (USPN 6,096,364).

Malterud et al. teach the complete list of polymethoxylated flavonoids as disclosed in instant claim 15, such as sinensetin, nobiletin, tangeretin, heptamethoxvflavone and tetramethylscutellarein (as disclosed in instant claim 15), which have been isolated from orange peel and collectively are inhibitors of 15 lipoxygenase (lines 1-6).

Malterud et al. further teaches that [these] orange peel constituents may counteract enzymatic lipid peroxidation processes catalyzed by 15-lipoxygenase in vitro (lines 17-21).

Thus, Malterud et al. teach inhibitors of lipoxygenase, which is connected to Type 2 diabetes, which is consequently the disease to which insulin resistance progresses. Specifically, increased production of 15-lipoxygenase adversely affects insulin resistant/Type 2 diabetic patients. Insulin resistance is normally a precursor adverse affect, which progresses into Type 2 diabetic patients.

Manthey et al. teach several polymethoxylated flavones comprising tangeretin, nobiletin, sinensetin and heptamethoxyflavone (with the exception of tetramethylscutellarein) and a practicing disclosure of dosing parameters (column 3, lines 42 – 54). Generally, the dose of the polymethoxylated flavones given in the methods of the present invention (i.e., the effective amount of a polymethoxylated flavone) are at a quantity that results in a reduction in the concentration or in vivo amount of cytokines (e.g., tumor necrosis factor, alpha. interleukin-10, macrophage inflammatory protein-1.alpha. and the like; especially tumor necrosis factor. alpha.) in the mammal. Preferably, the dose is a cytokine production-inhibiting amount (e.g., a quantity of polymethoxylated flavones capable of inhibiting the production of the cytokines or reducing the amount produced or the rate of production of the cytokines). Methods of determining the effective concentrations are well known in the art. For example, a person of ordinary skill in the art can easily extrapolate the effective concentrations as determined in vitro and apply it to living mammals to determine the effective concentrations in vivo. Likewise, the disclosure of 26% in instant claim 15 would thereby encompass and overcome subject claim by way of obviousness via necessity of extrapolation of effective concentrations to achieve claimed reduction of serum insulin levels. Preferably, the dose of the polymethoxylated flavone is between 0.1-10 grams per 100 Kg body weight; most preferably between 1-10 grams per 100 Kg body weight (column 4,

lines 19 – 36). Instant claims 21 and 22 disclose a PMF composition of which up to 5000 mg/day may be administered and said composition being administered in a specific dosage of 70mg/kg/day, based on weight of said mammal, respectively. Accordingly, Manthey et al. teach the various administration routes of polymethoxylated flavones, such as oral, transdermal, subcutaneous, rectal, intraarticular, intravenous and intramuscular introduction, that are obvious over instant claims 21 and 20, which disclose same routes for said agent.

Manthey et al. do not teach a method for preventing insulin resistance nor does it teach on tetramethylscutellarein, a polymethoxylated flavone as disclosed in instant claim 15.

Bok et al. teach a method for lowering blood glucose levels in diabetic patients by the administration of bioflavonoid. The polymethoxylated flavones taught are nobiletin, sinensetin, and tangeretin (column 1, Table I).

Bok et al. do not specifically teach a method of reducing insulin resistance nor does it teach on tetramethylscutellarein or heptamethoxyflavone as disclosed in instant claim 15.

Further for evidentiary purposes, Type 2 diabetes is associated with significantly accelerated rates of macrovascular complications such as atherosclerosis. Atherosclerosis is an inflammatory disease and, therefore, certain inflammatory markers may be key predictors of diabetic atherosclerosis. Proinflammatory cytokines and cellular adhesion molecules expressed by vascular and blood cells during stimulation by growth factors and cytokines seem to play major roles in the pathophysiology of atherosclerosis and diabetic vascular complications. However, more recently, data suggests that inflammatory responses can also be elicited by smaller oxidized lipids that are components of atherogenic oxidized low-density lipoprotein or products of phospholipase activation and arachidonic acid metabolism. These include oxidized

lipids of the lipoxygenase and cyclooxygenase pathways of arachidonic acid and linoleic acid metabolism. These lipids have potent growth, vasoactive, chemotactic, oxidative, and proinflammatory properties in vascular smooth muscle cells, endothelial cells, and monocytes. Cellular and animal models indicate that these enzymes are induced under diabetic conditions, have proatherogenic effects, and also mediate the actions of growth factors and cytokines. This review highlights the roles of the inflammatory cyclooxygenase and 12/15-lipoxygenase pathways in the pathogenesis of diabetic vascular disease (Natarajan et al., Lipid Inflammatory Mediators in Diabetic Vascular Disease, Arteriosclerosis, Thrombosis, and Vascular Biology, 2004; 24:1542, printed pages 1 and 2, see pages 1 and 2).

Inflammatory responses in the vasculature can be elicited by small-oxidized lipids that are components of oxidized low-density lipoprotein or products of the lipoxygenase and cyclooxygenase pathways of arachidonic and linoleic acid metabolism. This review evaluates these inflammatory and proatherogenic pathways in the pathogenesis of diabetic vascular disease (Natarajan et al., Lipid Inflammatory Mediators in Diabetic Vascular Disease, Arteriosclerosis, Thrombosis, and Vascular Biology, 2004; 24:1542, printed pages 1 and 2, see page 2).

Thus, it is prima facie obvious to combine and/or incorporate together the teachings of Malterud et al., Manthey et al., and Bok et al., via the motivation to combine by Malterud et al. Malterud et al. teach the complete disclosure of polymethoxylated flavones as disclosed in instant claim 15. As comprised in instant claim 15 for insulin resistance, the five disclosed polymethoxylated flavones are taught as a group comprising thereof for inhibition of 15-lipoxygenase. One of ordinary skill in the pertinent art at the time of the instant invention would instantly recognize the motivation to incorporate and modify the teachings of Manthey et al. and

Bok et al. with the addition of Malterud et al. (incorporating the addition of tetramethylscutellarein). Accordingly, The radical –scavenging activity of the five instant polymethoxylated flavones disclosed results in a practicing method of reducing 15- lipoxygenase (Hatley et al. Increased production of 12/15 lipoxygenase eicosanoids accelerates monocyte/endothelial interactions in diabetic db/db mice. J Biol Chem. 2003 July 13; 278(28): 25369-75, printed pages 1 and 2, see page 1). One of ordinary skill in the pertinent art would have had a reasonable expectation of successfully combining the method of Manthey et al. and the method of Bok et al., (as both teach the administration of polymethylated flavones (bioflavonoids)). Malterud et al. is the motivation to combine due to 1) the five identical bioflavonoid agents as disclosed and taught in instant invention and Malterud et al., and 2) the five identical bioflavonoid agents with indication of therapy for inhibiting an enzyme, which has direct correlation to insulin resistance as disclosed in instant invention. This rejection is necessitated by amendment.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Malterud et al., Manthey et al., and Bok et al. as applied to claims 15 and 20-23 above, and further in view of Pershadsingh et al. (USPN 6,087,385) and Robbins (USPN 3,867,541).

Pershadsingh et al., teach tangeretin sensitizing and the reduction of insulin resistance (including diabetes) (Abstract, column 1, lines 20-40).

Pershadsingh et al. does not teach tangeretin or any other agents in its class as a single or combination therapy for insulin resistance. However, instant claim 25 discloses a polymethoxylated flavone composition comprising said agent or agents. Therefore, instant claim

25 suggests that the polymethoxyflavone composition could instantly comprise one said polymethoxyflavone and some other agent in order to mitigate insulin resistance.

Robbins teaches methoxylated flavonoids having at least two methoxyl radicals or substituents exhibiting powerful anti-adhesive effects on blood cells in vivo and in vitro. Such flavonoids are combined with an anticoagulant therefore providing greater protection against thrombi formation than when either is used without the other. Instant specification discloses an etiology of insulin resistance, which includes impairment of endothelium-dependent vasodilation, and a reduction in nitric oxide, which is an important mediator involved in protection against atherosclerosis. Insulin resistance syndrome commonly precedes type 2 diabetes and both disorders are associated with the increased risk of heart disease (specification [0002] and [0003]). The teaching of Robbins overcomes instant claim 25 in the way of obviousness. Instant specification fails to disclose the reason of specificity in percentages of disclosed polymethoxylated flavones, however one of skill in the art would instantly recognize the necessity to extrapolate magnitudes for an efficacious therapeutic concentrations of components of said formulation.

Thus it would have been obvious to one of ordinary skill in the pertinent art at the time of the invention to have modified and/or combined the methods and teachings of Robbins and Pershadsingh et al. The instant invention is drawn toward a method of treating a mammal having metabolic abnormalities resulting from insulin resistance comprising administering an effective amount of polymethoxyflavone composition comprising sinensetin, nobiletin, tangeretin, heptamethoxvflavone and tetramethylscutellarein to reduce serum insulin levels by at least about 26% (instant claim 15). One of ordinary skill in the art would have had a reasonable expectation

of successfully combining and/or modifying Robbins and Pershadsingh et al. which both essentially teach practicing polymethoxylated flavones and methods of administration thereof. This rejection is necessitated by amendment.

Further, in view of all references cited *supra,* the deficiencies of the Malterud et al. reference are adequately elucidated by Manthey et al. and Bok et al. Malterud et al adequately satisfy the deficiencies of Manthey et al. and Bok et al. Malterud et al. essentially teaches each and every polymethoxyflavonoid in view of the instant invention. Further motivation to combine is contained in the following:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

11/10/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER